Features of Resolving and Nonresolving Indeterminate Pulmonary Nodules at Follow-up CT: The NELSON Study

Ying Ru Zhao, MD
Marjolein A. Heuvelmans, BSc
Monique D. Dorrius, MD, PhD
Peter M. A. van Ooijen, PhD
Ying Wang, MD, PhD
Geertuida H. de Bock, PhD
Matthijs Oudkerk, MD, PhD
Rozemarijn Vliegenthart, MD, PhD

Purpose:
To retrospectively identify features that allow prediction of the disappearance of solid, indeterminate, intraparenchymal nodules detected at baseline computed tomographic (CT) screening of individuals at high risk for lung cancer.

Materials and Methods:
The study was institutional review board approved. Participants gave informed consent. Participants with at least one noncalcified, solid, indeterminate, intraparenchymal nodule (volume range, 50–500 mm³) at baseline were included (964 nodules in 750 participants). According to protocol, indeterminate nodules were re-examined at a 3-month follow-up CT examination. Repeat screening was performed at years 2 and 4. A nodule was defined as resolving if it did not appear at a subsequent CT examination. Nodule resolution was regarded as spontaneous, not the effect of treatment. CT features of resolving and nonresolving (stable and malignant) nodules were compared by means of generalized estimating equations analysis.

Results:
At subsequent screening, 10.1% (97 of 964) of the nodules had disappeared, 77.3% (n = 75) of these at the 3-month follow-up CT and 94.8% (n = 92) at the second round of screening. Nonperipheral nodules were more likely to resolve than were peripheral nodules (odds ratio: 3.16; 95% confidence interval: 1.76, 5.70). Compared with smooth nodules, nodules with spiculated margins showed the highest probability of disappearance (odds ratio: 4.36; 95% confidence interval: 2.24, 8.49).

Conclusion:
Approximately 10% of solid, intermediate-sized, intraparenchymal pulmonary nodules found at baseline screening for lung cancer resolved during follow-up, three-quarters of which had disappeared at the 3-month follow-up CT examination. Resolving pulmonary nodules share CT features with malignant nodules.

1 From the Center for Medical Imaging–North East Netherlands (Y.R.Z., M.A.H., M.D.D., P.M.A.v.O., Y.W., M.O., R.V.), Department of Radiology (Y.R.Z., M.A.H., M.D.D., P.M.A.v.O., R.V.), and Department of Epidemiology (G.H.d.B.), University of Groningen, University Medical Center Groningen, Hanzeplein 1, Postbus 30.001, 9700 RB Groningen, the Netherlands. From the 2012 RSNA Annual Meeting. Received February 8, 2013; revision requested April 3; revision received August 1; accepted August 20; final version accepted August 27. Supported by Zorg Onderzoek Nederland-Medische Wetenschappen (ZonMw), KWF Kankerbestrijding, Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen (Rvz).

Address correspondence to R.V. (e-mail: r.vliegenthart@umcg.nl).

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With the widespread use of multidetector computed tomography (CT) in daily clinical practice and in screening for lung cancer, the number of detected pulmonary nodules has increased compared with those found at standard chest radiographic examinations. Up to 66% (1) of participants enrolled in CT screening trials have at least one small- to intermediate-sized pulmonary nodule. Solid lung nodules are the most common type of nodules found at lung cancer screening (2,3). Most indeterminate nodules are benign (2) and may represent granulomatous or infectious lesions or enlarged lymph nodes. It is not clear whether it is possible to identify the specific features of nodules that will subsequently resolve to avoid unnecessary repeat CT scans and work-up, public health costs, and patient anxiety.

Four studies (4–7) of resolving nodules have been performed, but only one of these studies (4) was focused on solid lung nodules. However, a substantial portion of the follow-up examinations in this study was performed with thicker sections, which may allow small remaining lesions to be missed. Also, this study did not include a comparison of resolving with nonresolving nodules.

The Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) is the first in which nodule management is based on CT-derived volume and volume doubling time assessment (8). Volume measurements for newly detected nodules and growth evaluation of previously detected nodules was previously published in detail (8). The purpose of our study was to retrospectively identify features that allow prediction of the disappearance of solid, indeterminate (volume, 50–500 mm³), intraparenchymal nodules detected at baseline CT screening in individuals at high risk for lung cancer.

### Materials and Methods

#### Study Population

This study was performed in the context of the NELSON trial, (trial registration number, ISRCTN63545820), which was approved by the Dutch Health Care Committee and the ethics board at each participating center. All participants gave written informed consent at study entry. Our retrospective evaluation fell under the terms of the informed consent of the NELSON study. Participants were 46–76 years old and were recruited by using population registries through mail. Only current or former smokers with a smoking history of greater than 15 cigarettes per day for more than 25 years or greater than 10 cigarettes per day for more than 30 years were included. People with a history of pneumonectomy, breast cancer, melanoma, or hypernephroma were not included. People with a history of other types of cancer were only eligible if they were curatively treated at least 5 years ago without signs of recurrence at the time of inclusion (12). Participants underwent low-dose multidetector CT screening at baseline (first round), 1 year later (second round), and 3 years later (third round) and received extra low-dose follow-up multidetector CT if an indeterminate lung nodule was found. The NELSON screening protocol was previously published in detail (8).

Our study was based on all baseline examinations of the NELSON project. In total, 7557 participants underwent baseline screening between April 2004 and December 2006 (2). The mean age of participants was 59 years (range, 46–76 years). Sixteen percent (1247 of 7557) were women (mean age, 58 years; range, 46–75 years), and 84% (6310 of 7557) were men (mean age, 59 years; range, 46–76 years).

According to the NELSON protocol, noncalcified solid nodules were classified into categories on the basis of size (8). A previous study (13) showed that
the rate of malignancy in attached indeterminate lung nodules was negligible. Therefore, in our study, only solid intraparenchymal (ie, surrounded by lung parenchyma) nodules with volumes of 50–500 mm³ (ie, intermediate size) at baseline screening were included. Patients with larger nodules were referred to a pulmonologist and smaller nodules did not receive extra follow-up. An indeterminate result led to an extra follow-up CT examination 3 months after baseline. If no growth or slow growth of the nodule was found, subjects subsequently underwent the standard repeat screening examination. Indeterminate nodules without substantial growth at least 2 years after baseline or with a benign result at histologic analysis were regarded as benign. Subjects with a fast-growing nodule (volume doubling time < 400 days) were referred to a pulmonologist for further diagnosis.

Nodules with less than 2 years of follow-up after baseline were excluded. Also, participants with malignancies other than primary lung cancer were excluded.

CT Scanning Protocol
At all four screening sites, 16-channel multidetector CT scanners were used (Sensation-16, Siemens Medical Solutions, Forchheim, Germany; or Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, Ohio). Scanning of the entire chest was performed in the caudal-to-cranial direction. Scanning data were obtained in spiral mode, with 16 × 0.75 mm collimation and 1.5 pitch. No contrast material was used. Low-dose settings were applied depending on body weight (< 50 kg, 50–80 kg, and > 80 kg), with kVp settings of 80–90, 120, and 140 kVp, respectively, to achieve a CT dose index volume of approximately 0.8 mGy, 1.6 mGy, and 3.2 mGy, respectively. The milliamperesecond settings were adjusted accordingly, depending on the system used. To minimize breathing artifacts, CT scanning was performed at suspended maximal inspiration after appropriate instruction of the subjects. Data were reconstructed with a section thickness of 1.0 mm, with a 0.7-mm reconstruction increment. Repeat examinations were performed with the same parameters as those used at baseline.

Image Reading
All CT images were read twice independently (2,8). First readings were done by one of 13 radiologists with experience of 1 to more than 20 years in thoracic CT. Second readings were done by one of two radiologists (Y.W. and Y.R.Z., with at least 6 years of experience). When there was a discrepancy between the readings of the two radiologists, a third radiologist (M.O., with more than 15 years of experience in thoracic CT) arbitrated. Discrepancy in nodule categorization between first and second reading was found for 43 lesions in 37 individuals.

The Syngo Lungcare software package (Leonardo workstation, Somaris/5 VB 10A; Siemens Medical Solutions, Erlangen, Germany), which was designed to aid radiologists in diagnosing pulmonary nodules, was used in addition to visual evaluation. Baseline and follow-up images were reviewed and displayed simultaneously on one workstation. Lung windows were assessed at a width of 1600 HU and a level of −700 HU. All images were interpreted both in lung window and mediastinal settings. First, the reader detected the pulmonary nodule and marked it with a mouse click. Subsequently, the program automatically defined the volume of interest of the nodule. A three-dimensional template was generated to represent the nodule optically. If needed, manual modification of the segmentation was performed. A second mouse click initiated the automated volume measurement program. Semiautomated measurements are highly reproducible for most nodules (14). In 86% of more than 4000 screening-detected solid nodules, double reading yielded the same volume. Volume differences of more than 15% were found in only 4% of the nodules (14). If volume measurements of the readers differed, the results determined by the second reader were used for further analyses.

Nodule Characteristics
Nodules were classified as benign or malignant on the basis of histologic examination or as benign on the basis of stable volume for more than 2 years after baseline. In addition, they were classified on the basis of distance to costal pleura (peripheral or nonperipheral), shape (spherical or nonspherical), and margin (smooth, lobulated, spiculated, or irregular) (8,13,15).

The distance to costal pleura was less than one-third of the total distance to hilum-costal pleura for peripheral nodules and more than one-third for nonperipheral nodules. A nodule was regarded as nonsmooth when its margin was lobulated, irregular, or spiculated, and if otherwise, it was considered smooth (15,16). A nodule was regarded as spherical when its maximum diameter was smaller than twice its minimum diameter; otherwise, it was considered nonspherical.

Nodule Resolution
At follow-up examinations, images were compared with those of the previous screening round. A nodule was defined as completely resolving if it had disappeared at a follow-up examination, otherwise, it was considered nonresolving. In the NELSON study, a 25% change in nodule volume was used to differentiate real change from measurement variation (11). Thus, decrease in volume of 25% or more was regarded as an actual decrease in size. Nodules that decreased in size but did not disappear were regarded as nonresolving because nodules that decrease at some point can eventually become malignant (17). Nodule resolution was regarded as spontaneous and not the effect of treatment because antibiotic therapy was not part of the nodule management protocol.

Statistical Analysis
Generalized estimating equation analyses with a logit link function and a binomial distribution were performed to assess whether nodule characteristics were related to disappearance at 3-month follow-up CT, and regular screening CT rounds at years 2 and...
At the baseline examination, 1059 solid intraparenchymal nodules with a volume of 50–500 mm³ were found in 805 participants. Ninety five nodules in 55 participants were excluded: -88 (52 participants): no histology obtained and < 2 years follow-up - 6 (2 participants): metastatic disease - 1 (1 participant): mesothelioma

97 (10.1%) nodules in 75 participants disappeared: 75 (77.3%) disappeared at month 3 17 (17.5%) disappeared at year 2 5 (5.2%) disappeared at year 4

867 (89.8%) nodules in 695 participants did not disappear: 840 (96.9%) benign 27 (3.1%) malignant

4 after the baseline examination. For distance to costal pleura, shape, and margin, the odds ratios and 95% confidence intervals were estimated by means of univariate analyses. Then, multivariate analysis of the combined factors was performed, with adjustments for the potential confounding effects of age and sex. χ² testing was used to compare the rate and timing of disappearance for nodules with maximal transverse diameter smaller than 8 mm and those 8 mm or larger (18) on the basis of semiautomated volumetry. A P value less than or equal to .05 was considered to indicate a statistically significant difference. All statistical analyses were performed by using SPSS 20.0 (SPSS, Chicago, Ill).
with nonspherical shape tended to have a lower chance of resolution than did spherical nodules (odds ratio: 0.53; 95% confidence interval: 0.23, 1.21).

In analysis according to maximum diameter (< 8 mm vs ≥ 8 mm), the rate of disappearance was lower for nodules smaller than 8 mm than for nodules 8 mm or larger (Table 3). A higher percentage of the larger nodules disappeared before the short-term follow-up CT examination than did the smaller nodules (Table 4).

**Figure 2**: CT images show examples of resolving nodules. (a) Smooth and round nodule (arrow) with (b) baseline volume of 106.2 mm$^3$ (c) disappeared at 3-month follow-up, and (d) lobulated nodule (arrow) with (e) baseline volume 167.3 mm$^3$ (f) disappeared at 3-month follow up.
Table 2

Baseline Characteristics and Disappearance of Solid Intraparenchymal Nodules

<table>
<thead>
<tr>
<th>Nodule Characteristic at Baseline</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>P Value</td>
</tr>
<tr>
<td>Distance to costal pleura</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Non peripheral</td>
<td>3.03 (1.73, 5.29)</td>
<td>.12</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spherical</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nonspherical</td>
<td>0.54 (0.24, 1.19)</td>
<td>.09</td>
</tr>
<tr>
<td>Margin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lobulated</td>
<td>1.50 (0.83, 2.73)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>vs spiculated</td>
<td>.32</td>
<td>.49</td>
</tr>
<tr>
<td>vs irregular</td>
<td>.18</td>
<td></td>
</tr>
<tr>
<td>vs smooth</td>
<td>.49</td>
<td>.66</td>
</tr>
<tr>
<td>Spiculated</td>
<td>4.37 (2.25, 8.48)</td>
<td>4.36 (2.24, 8.49)</td>
</tr>
<tr>
<td>vs irregular</td>
<td>.09</td>
<td>.09</td>
</tr>
<tr>
<td>vs smooth</td>
<td>.18</td>
<td>.12</td>
</tr>
<tr>
<td>Irregular</td>
<td>2.82 (0.86, 9.22)</td>
<td>3.12 (0.75, 12.99)</td>
</tr>
<tr>
<td>vs smooth</td>
<td>.09</td>
<td>.09</td>
</tr>
</tbody>
</table>
Note.—Data in parentheses are 95% confidence intervals. In the multivariate analyses, the nodule characteristics and participant age and sex were included as potential confounders.

Table 3

Nodule Resolution according to Nodule Size

<table>
<thead>
<tr>
<th>Maximal Transverse Diameter</th>
<th>Total</th>
<th>Resolving</th>
<th>Nonresolving</th>
<th>Nonresolving Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 mm</td>
<td>751</td>
<td>58 (7.7)</td>
<td>693 (92.3)</td>
<td>14 (2.0)</td>
</tr>
<tr>
<td>≥8 mm</td>
<td>213</td>
<td>39 (18.3)</td>
<td>174 (81.7)</td>
<td>13 (7.4)</td>
</tr>
<tr>
<td>Total</td>
<td>964</td>
<td>97 (10.1)</td>
<td>867 (89.9)</td>
<td>27 (3.1)</td>
</tr>
</tbody>
</table>
Note.—Data are number of nodules, with percentages in parentheses. A significant difference between resolving and nonresolving nodules and between nonresolving and nonresolving malignant nodules was found according to nodule size (P < .001 for both comparisons).

Discussion

From 2004 to 2006, 805 of 7557 participants (10.7%) in the NELSON study had at least one solid intraparenchymal nodule with a volume of 50–500 mm³. Of the 964 nodules that were included, 97 (10.1%) had disappeared at follow-up examination. Although most solid indeterminate intraparenchymal pulmonary nodules found at baseline lung cancer screening do not resolve, 75% of the nodules that do resolve can be identified at short-term repeat CT examination. Nonperipheral nodules were three times more likely to resolve than were peripheral nodules. Spiculated nodules had a four times higher chance of disappearing than did smooth nodules.

Few studies of lung cancer screening have been focused on disappearing nodules. Diederich et al (4) studied 107 resolving nodules in 56 individuals. Lee et al (5) studied 126 resolving part-solid nodules in 93 subjects. Felix et al (6) evaluated 32 resolving ground-glass opacity nodules in 18 subjects, and Mario et al (7) assessed 18 of 76 resolving ground-glass opacity nodules. Nonsolid and part-solid nodules have different characteristics than do solid nodules.

In the study by Diederich et al (4), the number of resolving nodules per individual was 2.38 for participants who had at least one resolving nodule. In that study, the maximum diameter of completely resolving nodules was 5 mm or smaller in 56 of 107 (52%) nodules. For nodules smaller than 5 mm, even those that persist have negligible risk of malignancy (19). In our study, including nodules with volumes of more than 50 mm³ (corresponding to a diameter of 4.6 mm), only two of 964 (0.002%) nodules measured 5 mm or less. Diederich et al (4) found most of the completely resolving nodules in participants younger than 50 years. The risk of lung cancer development increases with age (20). In this study, the mean age of subjects was 60 years ± 6, with an age distribution comparable to the overall age distribution of the NELSON study (2). Therefore, our results mainly concern the behavior of lung nodules with an intermediate risk (based on size and age) of being malignant.

In the study by Diederich et al (4), more than one resolving nodule was found in 34% of the subjects, and in one individual, more than 13 resolving nodules were identified. In our study, the number of resolving nodules per individual was lower (1.32 per individual) due to the exclusion of small and large nodules. Twenty percent of the subjects had more than one nodule that disappeared (range, two to five) (4). In addition to the explanations of nodule size and age, another possible explanation is that these nodules represented the end stage of benign diseases because multiple nodules are often seen in patients with emphysema or inflammation.

Even in patients at high risk of developing lung cancer, most incidentally detected nodules are benign (21). These benign nodules are probably caused by focal infection or inflammation and often have resolved completely or decreased in size at short-term follow-up either after therapy with antibiotics or spontaneously (22). Libby et al (23) from the Early Lung Cancer Action Project reported that 12% of nodules 5 mm or larger in diameter in participants who had received antibiotics had completely

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resolved 2 months after the initial CT baseline screening. Antibiotic therapy was not part of the NELSON protocol. Libby et al (23) reported direct referral for nodules larger than 15 mm, so the size of their group of nodules (5–15 mm), and therefore, the risk of infection or inflammation, did not differ much from those in our study (5–10 mm). Because the nodule disappearance in our study was not the effect of any treatment, our results showed a lower percentage (8%) of resolving nodules at short-term follow-up (3 months).

A solid, peripheral, subpleural nodule is a specific benign lesion, and most may represent intrapulmonary lymph nodes (16). The main proportion of resolving nodules in this study were peripheral. Both resolving and nonresolving nodules were mainly spherical. Nodules with a smooth margin were numerous in both the resolving and the nonresolving groups. However, the results showed significant differences between resolving and nonresolving nodules in nodule characteristics. Distance to the costal pleura and margin were correlated with nodule disappearance.

The characteristics of nodule edge are important in determining whether a lesion is benign or malignant. However, nodules in patients with benign conditions such as lipid pneumonia, tuberculosis, and progressive massive fibrosis may have spiculated margins similar to those of malignant nodules (24). Moreover, a lobulated outline is often associated with malignancy, but may be seen in up to 25% of benign nodules (25). Furuya et al (26) analyzed margin characteristics of pulmonary nodules at thin-section CT and found that 80% of the polygonal nodules were the result of inflammatory change, and 20% represented primary lung cancer. According to the results of the study by Takashima et al (27), concave margin and polygonal shape were both specific to benign lesions. Our results also showed that nodules with nonsmooth edges disappeared more frequently than did those with smooth edges. However, nonsmooth edges are also more frequently found in malignant nodules (28). So, on the basis of the characteristics of nodule edge, no differentiation can be made between resolving and nonresolving malignant nodules.

The rate and speed of disappearance were higher in baseline-detected nodules with a larger diameter (≥ 8 mm vs < 8 mm). However, the rate of malignancy was also higher. Some benign conditions like inflammation commonly show nodules with a larger diameter. This may be an explanation for the increased probability of disappearance of nodules with larger maximal transverse diameter. Further stratification of indeterminate nodules dependent on diameter did not help in differentiating between resolving and malignant nodules, and, on the basis of our results, cannot substitute for the NELSON volume-based protocol.

An important topic in lung cancer screening is the interval of follow-up. The volume doubling times of most benign pulmonary nodules are more than 450 days, whereas volume doubling times of malignant lesions are usually less than 400 days (29). In several randomized controlled trials that are underway, the interval of early follow-up imaging is 3, 6, or 12 months (30–33). According to our screening protocol, patients with indeterminate nodules (volume, 50–500 mm³) underwent repeat CT 3 months after the baseline examination to detect growth. Our results showed that more than 75% of the resolving nodules had disappeared at the 3-month follow-up examination. Therefore, for indeterminate nodules detected at screening, a short-term follow-up after initial CT could exclude a considerable number of benign lesions from further workup.

A limitation of the current study was that the precise time of nodule resolution could not be ascertained, but only the period between the first CT at which the nodule was detected (in this study, the baseline examination) and the first CT examination after the nodule had completely disappeared. Meanwhile, histologic evidence could not be obtained for those resolving nodules. Whether our results can be generalized to nodules that are incidentally found in a nonscreening examination is yet to be proved. Further investigations should be performed to evaluate the applicability of the nodule management protocol as used in the NELSON study in clinical settings.

In conclusion, about 10% of solid intraparenchymal nodules of intermediate size (volume, 50–500 mm³) found at baseline lung cancer screening disappeared during follow-up. Our findings provide further support for a 3-month follow-up CT examination for indeterminate lung nodules. Short-term follow-up CT is valuable not only to detect fast growth by determining volume doubling time, but also to identify three-quarters of resolving nodules. Unfortunately, resolving pulmonary nodules share CT features with malignant nodules. Thus, nodule characteristics cannot sufficiently allow intermediate-sized nodules that will subsequently disappear to be distinguished from those that will not.

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Table 4

<table>
<thead>
<tr>
<th>Maximal Transverse Diameter</th>
<th>Total Resolving</th>
<th>3 Months</th>
<th>Year 2</th>
<th>Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 mm</td>
<td>58 (7.7)</td>
<td>40 (69.0)</td>
<td>14 (24.1)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>≥8 mm</td>
<td>39 (18.3)</td>
<td>35 (89.7)</td>
<td>3 (7.7)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Total</td>
<td>97 (10.1)</td>
<td>75 (75.8)</td>
<td>17 (17.2)</td>
<td>5 (5.0)</td>
</tr>
</tbody>
</table>

Note.—Data are number of nodules, with percentage in parentheses.
References